Selection bias may explain the relationship between coronavirus diagnosis and the odds of prior influenza vaccination

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In a previous message I discussed the relationship between serial influenza vaccine receipt and current year vaccine effectiveness (VE) [1]. The nuances of influenza VE estimation were not expanded upon in that message but two recent publications offer an opportunity to discuss this within the context of the current pandemic.

Ideally, medical intervention efficacy and effectiveness is most robustly estimated using a randomized control trial (RCT). For a number of reasons previously mentioned, including limited time course studies and antigenic drift across years, this may not be a feasible study design in the context of rapidly evolving pathogen and vaccine strains. Furthermore, application of an RCT to assess influenza VE across population strata is ethically complicated, given that the vaccine is recommended for certain at-risk groups [2]. This has led researchers, historically, to employ more novel study designs to examine these relationships.

A potential study design then may be a classical observational cohort study; wherein, a sample of individuals presenting with influenza-like illness (ILI) are separated into groups by exposure to influenza vaccine and influenza infection is then ascertained through laboratory confirmation (Figure 1).

However, setting vaccination status as the exposure and influenza diagnosis as the outcome presents a few issues that violate the assumptions of cohort studies. For a full description of these I refer readers to the informative descriptions provided by Fukushima and Hirota [2]. The salient point is that individuals in both arms of the cohort study, those vaccinated and unvaccinated, should have equal probability of entry into the study. Due to health-seeking behavior, those vaccinated may have a higher likelihood of a medical visit. To address the bias this unequal probability of sampling introduces the "test-negative" study design was developed and employed with much success [2, 3].

The test-negative study design overcomes this violation by setting influenza diagnosis as the exposure and vaccination status as the outcome in a modified case-control design (Figure 2). Individuals presenting with ILI to health care sites enrolled in the sentinel surveillance systems are first grouped by influenza diagnosis as cases (influenza positive) and controls (influenza negative), and vaccination status is subsequently ascertained as the outcome, independent of study inclusion probability by vaccination. While this study design does overcome some of the violations of the classic cohort design within the context of influenza VE, its successful employment requires an understanding of the underlying study design assumptions. A recent case highlights this importance.

A study by Wolff [4], using 2017–2018 influenza season data, employed such a test-negative design to assess influenza VE among United States Department of Defense personnel. Wolff analyzed for influenza vaccine exposure status among study subjects presenting with

FIGURE 1

A classical observational cohort study.

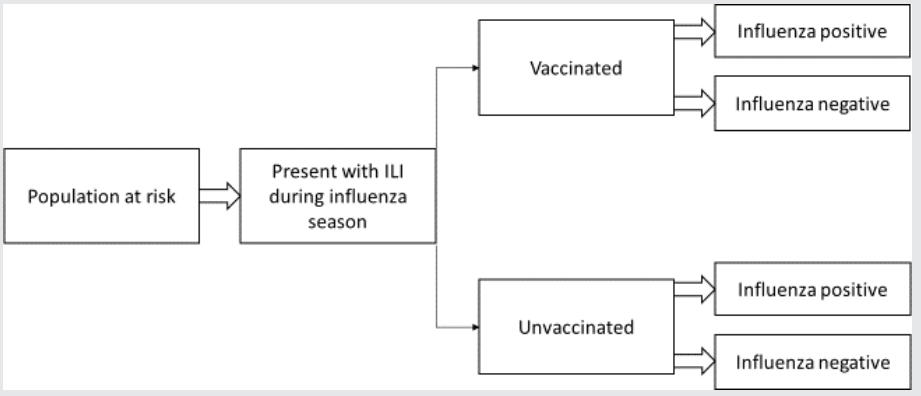

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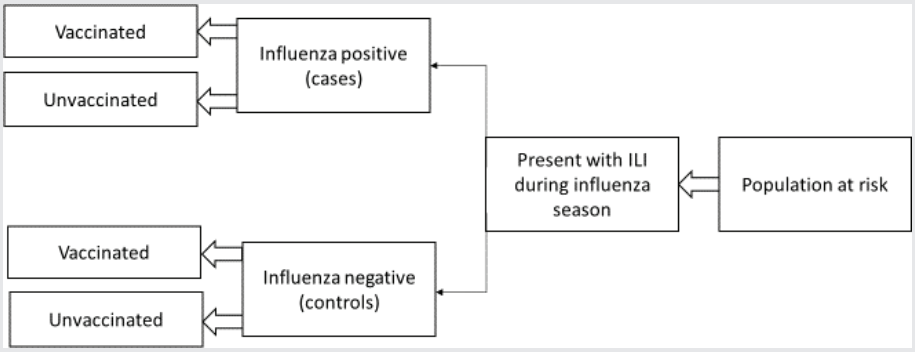
FIGURE 2

A test-negative study design.



ILI between those testing positive for combined noninfluenza respiratory virus (NIRV)—influenza-positive cases excluded—against those testing negative for influenza and other NIRVs tested (no respiratory virus detected). This analysis revealed a nonsignificant association between influenza vaccination and development of grouped NIRVs (adjusted odds ratio: 0.97, 95% confidence interval: 0.86–1.09), i.e., suggestive of a non-significant association between influenza vaccination status and development of NIRVs. In further unadjusted analyses of the association of influenza vaccination status against specific NIRVs—such as adenoviruses, coronaviruses, rhinoviruses, etc.—Wolff found a greater odds of influenza vaccination among those diagnosed with coronaviruses, suggestive of a greater risk of coronavirus infection among those vaccinated against influenza (unadjusted odds ratio: 1.36, 95% confidence interval: 1.14–1.63)[4]. The author cites the theory of vaccine interference as a possible explanation for this finding: influenza infection may offer innate, nonspecific immunity against other NIRV [2, 4, 5].

This finding went relatively unnoticed for a short period, until around March 2020, when the gravity of the COVID-19 disease pandemic was beginning to be appreciated in North America. The findings of Wolff's study [4] began circulating around social media, with claims that influenza vaccination would lead to a greater risk of SARS-CoV-2, the causative agent of COVID-19 disease. This prompted both a letter to the editor in *Vaccine* as well as an article by the fact-checking site, Snopes, to address the validity of these claims [6]. Both rightly identify that Wolff's analyses did not include testing for SARS-CoV-19, which had not been isolated at the time of data collection. However, further examination of the methods employed in the study reveal selection bias as a possible source of spurious findings.

In a study published online (at the time of writing), ahead of print, Skowronski and colleagues [5] uncovered a major violation of an assumption of test-negative design used by Wolff: "that vaccine has no effect on alternate etiologies of the same clinical syndrome included in the control group." The authors noted that Wolff [4] excluded influenza-positive cases from his combined NIRV analysis but included these positive case in subanalyses of specific NIRVs. By doing so, Wolff biased his subanalyses, as influenza-positive cases within the control arm would have a lower likelihood of vaccination, thereby inflating the odds ratio of vaccine receipt within the coronavirus case group [5].

Accounting for this violation, Skowronski and authors [5] re-examined data collected during the 2010–2011 to 2016–2017 influenza seasons in Canada, correctly excluding influenza-positive cases from analysis, and found no significant association between coronavirus diagnosis and influenza vaccination (odds ratio: 1.04, 95% confidence interval: 0.85–1.28). It's also important to note that these findings say nothing about the effect of within-year influenza vaccination status against SARS-CoV-19.

These divergent findings highlight the importance of adherence to the principals of specific study design, and how violations of such can lead to spurious results. But perhaps more insidious is the effect that poorly conducted science can have on the degradation of faith in public health measures. As clinicians, educators, and researchers, it is our responsibility to ensure the information that we provide is accurate to the best of our knowledge. We are also trusted to translate and interpret knowledge produced from clinical research to a lay audience. As such, we should feel compelled to continuously advance our understanding of the nuances of the research that inform clinical guidelines and public policy so that we can appropriately critique information within the public sphere.

We've seen a bit of a swell in interest in respiratory therapy and cardiopulmonary medicine over the past months. With this interest comes the responsibility to interpret and translate detailed and often esoteric health and research information to a wider audience. I encourage the reader to continue to stay informed on the ongoing pandemic situation with a critical eye.

I also want to take this opportunity to thank the front-line workers across the world for their diligence, passion, and unending resolve in combatting this disease in the face of the most significant global health crisis any of us have experienced. Your dedication and selflessness is an inspiration and your recognition is well-deserved!

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